REMARKS

Claims 21-24 are currently pending. Claims 22 and 23 have been withdrawn from consideration as being drawn to a non-elected invention, and claims 21 and 24 are rejected under 35 U.S.C. § 103(a). In view of the arguments below, Applicants respectfully request reconsideration on the merits of the application, withdrawal of the rejection and allowance of the claims.

Rejections under 35 U.S.C. § 103(a)

Caskey, GenBank, Fregeau, Kimpton and Urquhart

Claims 21 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Caskey et al. (U.S. Patent 5,364,759) ("Caskey"), in view of GenBank STR loci (Accession Nos. M68651, M25858, D00269 and X14720) ("GenBank"), and further in view of Fregeau et al. (Bio Techniques, Vol. 15, No. 1, pp. 100-119 (1993)) ("Fregeau"), or Kimpton et al. (PCR Methods and Applications, Vol. 3, pp. 13-22 (1993)) ("Kimpton"), or Urquhart et al. (Int. J. Leg. Med., Vol. 107, pp. 13-210 (1994)) ("Urquhart").

Claim 21 is directed to simultaneously determining the alleles present in at least three short tandem repeat (STR) loci comprising coamplifying a set of at least three specifically recited loci and evaluating the alleles present. Claim 24 is directed to determining alleles present in at least four short tandem repeat (STR) loci comprising coamplifying a set of at least four specifically recited loci and evaluating the alleles present, which set of at least four loci includes one of the sets of three loci recited in claim 21.

Caskey was characterized as disclosing amplifying STR sequences from a DNA sample and evaluating the amplification products. Caskey does teach the amplification of certain loci (i.e., HUMFABP, HUMTH01, and HUMHPRTB), each of which is used in certain combinations with two other loci in the instantly claimed invention. However, as the Examiner pointed out, Caskey does not teach any of the recited combinations of loci. The Examiner cites GenBank Accession Numbers as teaching certain other STR loci (HUMTPOX, HUMVWFA31, and HUMCSF1PO).

Caskey was further characterized as describing identification of STR sequences in GenBank, primer design and synthesis, PCR amplification, and detection of amplified product.

The Examiner then concluded that "the method by which Caskey derives primers for STR loci appears to be consistent with the method of the instant application." With due respect, the method of the instant application is not directed to methods of deriving primers for STR loci. Rather, Applicants have discovered, and now claim, methods employing specific combinations of loci that can be simultaneously determined in a multiplex reaction to determine the alleles present in those loci.

Fregeau, Kimpton and Urquhart are cited as teaching multiplex systems for amplifying certain STRs, as well as primers for amplifying specific STRs. The Examiner asserts that Fregeau, Kimpton and/or Urquhart provide one having ordinary skill in the art motivation to choose *any reasonable number of loci* in desired combinations and to implement the multiplex amplification by routine optimization of PCR methodology. The Examiner concluded that it would have been *prima facie* obvious to modify the teachings of Caskey with the disclosures of GenBank, Fregeau, Kimpton and/or Urquhart to obtain the claimed invention.

Applicants respectfully submit that **the prior art does not teach each and every limitation of claims 21 and 24**. Specifically, as the Examiner has acknowledged, none of the references or any combination of references teaches or suggests using the specifically claimed combinations of loci.

Applicants respectfully submit that **there is no teaching, suggestion or motivation to modify the references to make the claimed invention.** Applicants submit that there is no suggestion or motivation in the references themselves or to one of ordinary skill in the art to combine the references' teachings to result in the claimed methods. More particularly, the Examiner fails to consider whether the claimed invention as a whole would have been obvious in light of the references. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP § 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)).

Applicants acknowledge that at the time the invention was made, one skilled in the art may have been *interested* in identifying sets of loci that could be coamplified. However, none of the references cited provides any teaching or suggestion to make the *particular combinations* of

STR loci used in the currently claimed methods. In fact, Caskey estimated that the human genome contains approximately 400 million STRs (Col. 10, line 15). Fregeau estimated the number of STRs within the human genome at approximately 500,000, including 6000-10,000 trimeric and tetrameric repeats (p. 101, column 1, first full paragraph). Caskey, which was filed on January 31, 1991, reported that there were 101 trinucleotide and 67 tetranucleotide STRs in GenBank at that time. Given the very large number of possible combinations of at least three loci that could be made using only those 168 trinucleotide and tetranucleotide repeat loci reported in GenBank as of 1991, the cited art does not provide motivation to modify the prior art references to arrive at a method employing the particular combinations of loci claimed.

Although the cited references may teach various methods of evaluating amplification products for identification by obtaining a DNA sample and amplifying STR sequences from the DNA sample, none of the cited references provides any motivation to use the specific claimed combinations of loci. Although GenBank may disclose the sequences of a few of the individual STR loci contained within the claimed groups of loci, it fails to provide one of ordinary skill in the art any suggestion or motivation to use the disclosed loci in methods such as those provided in claims 21 and 24. The lack of motivation to combine is particularly critical in light of the fact that, at the time the application to which the present application claims priority was filed, very few of the loci, and none of the claimed combinations of loci, were known to be useful for any purpose (e.g., genetic identity testing).

Furthermore, Applicants maintain that **the prior art provides no reasonable expectation of success**. The Examiner alleges "Caskey provides methods for choosing primers for use in multiplex analysis" and that the specification of the present application provides that "successful combinations are generated by trial and error [] of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified." (Office Action, p. 9). Applicants remind the Examiner that the reasonable expectation of success must be found in the prior art, not in applicant's disclosure. *See* MPEP § 2143 ("[T]he reasonable expectation of success must [] be found in the prior art, not in the applicants disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Thus, reliance on Applicants' specification as evidence that one having ordinary skill in the art, at the time the application to which the present application claims priority was filed, would have had a reasonable expectation of success when performing all of the limitations of the rejected claims is

improper. Applicants' disclosure may not be used as evidence to support the presence of a reasonable expectation of success.

Applicants maintain that one would not have had a reasonable expectation of success of making the claimed invention when performing all of the limitations of the rejected claims. Attached hereto and incorporated by reference herein is the declaration of Cynthia Sprecher, and inventor of the claims of the instant application. Ms. Sprecher attests that, at the time the application to which the present application claims priority was filed, one having ordinary skill in the art could not predict that any of the claimed methods, which require selecting the specific claimed sets of STR loci capable of being co-amplified, co-amplifying sets of loci in a multiplex amplification reaction, and evaluating the amplified alleles in the set to determine the alleles present at each of the loci in the set, would work with any reasonable expectation of success.

More specifically, Ms. Sprecher asserts that "at the time the application to which the present application claims priority was filed, few of the loci and none of the combinations of loci were 'known,' *per se*, to be useful for genetic identity purposes," "discovery of the usefulness of loci and combinations of loci claimed in the present application required inventive skill," "selecting STR loci for DNA typing, and subsequently co-amplifying the selected STR loci in a multiplex reaction, was very laborious and unpredictable" and "[i]t was virtually impossible to predict in advance which loci could be amplified and evaluated together in a multiplex reaction." (Declaration, pp. 3-4.) In fact, Ms. Sprecher states that "it was very possible that despite extensive trial and error, one having ordinary skill in the art would not have been successful in identifying useful multiplexes for DNA typing purposes." (*Id.*, p. 4.) Ms. Sprecher concludes that, for the various reasons discussed above, "none of the references and/or disclosures cited in the Office Action combine to teach or suggest the methods as defined by claims 21 and 24." (Declaration, p. 4.)

Finally, the cited references themselves indicate that one having ordinary skill in the art would not have had a reasonable expectation of success when selecting among the various known loci to result in a successful combination for use in a multiplex assay. For example, in order for a multiplex analysis to be useful, each locus contained within the assay must be different and unique among individuals within a large population. *See* Caskey, col. 22, ll. 24-27 (the loci selection process must consider "population heterogeneity, population allele

frequencies, [and] Mendelian inheritance"). Thus, one cannot simply randomly select a few loci out of all of those disclosed, most of which would not be useful for forensic analysis, and reasonably expect to result in a useful and successful combination. *See* Caskey, col. 10, ll. 14-17 ("These hybridization results and the results from the GenBank studies suggest the presence of approximately 400 million STRs in the human genome."); U.S. Patent 6,221,598 ("the '598 patent"), col. 1, ll. 32-37 ("It is estimated that there are 2,000,000 expected trimeric and tetrameric STRs present as frequently as once every 15 kilobases (kb) in the human genome." "Nearly half of the STR loci . . . are polymorphic."). In fact, the disclosures in GenBank may not even be accurate, further complicating the selection process. Urquhart, p. 16, col. 1 ("Sequencing the D21S11 locus also allowed us to make 2 amendments to the GenBank sequence."; "a TCCATA hexanucleotide was found which does not appear in the GenBank sequence").

Another challenge in creating a useful multiplex assay, which points away from a reasonable expectation of success, includes selecting loci combinations that produce allele patterns that are easy to distinguish and interpret. *See, e.g.*, Caskey, col. 2, ll. 58-59; col. 20, ll. 48-50 (loci combination was successful because the "STRs are amplified with great fidelity and the allele patterns are easily interpreted"; "the loci are selected such that the amplification products run in non-overlapping regions of the gel"); Fregeau, p. 117, col. 3; p. 104-05 ("the careful selection of . . . appropriate STR loci that have allele size ranges that are mutually resolvable" is important; "Ideally, both STR alleles generated from a heterozygous sample should yield a fluorogram of uniform intensity."). Further, each locus must have a low mutation rate (*i.e.*, be stable) and the loci combinations must produce precise and reproducible results. *See, e.g.*, Caskey, col. 22, ll. 24-25 ("locus stability" allows for "precise allele determination"); Fregeau, p. 117; p. 104, col. 3 (the "search for sensitive detection of polymorphic alleles has often created the challenge of obtaining allelic profiles"; the "demands for reproducibility, accuracy and precision . . . continue to be major governing factors dictating the progress" for DNA typing; an obstacle in multiplexing is deriving "a consistent and reliable allelic profile").

Also, according to several of the references, in order to obtain a successful STR loci combination, the loci must co-amplify to produce high fidelity both individually and collectively. *See, e.g.*, Urquhart, p. 18, col. 2 ("major considerations for selection of loci" include "discriminating power, absence of linkage, agreement with Hardy-Weinberg equilibrium, low

levels of 'shadow bands' (Hauge and Litt 1993), compatibility with other loci (for a multiplex system) and accurate sizing of alleles"); '598 patent, col. 6, ll. 5-17 ("[p]rior to constructing the multiplex system, an appropriate set of loci, primers, and amplification protocols must be selected such that amplification generates fragments such that alleles of the various loci do not overlap in size"; "the selected loci must be compatible for use with a single amplification protocol"; "Combinations of loci may be rejected . . . because, in combination, one or more of the loci do not produce adequate product yield, or fragments which do not represent authentic alleles are produced in this reaction.").

Moreover, in addition to all of the obstacles discussed above, at least two of the references discuss problems that arose when applying known techniques in order to create a successful loci combination. *See, e.g.*, Fregeau, p. 115, col. 2, p. 104, col. 2 ("The sharp contrast in efficiency of the amplification process noted using the theoretical maximum annealing temperature according to Wu and associates [*i.e.*, known method] and the empirically derived optimal annealing temperatures used in this study remains puzzling."; "Table 2 presents the estimated maximum annealing temperatures calculated according to the Wu equation [which yielded no or little product] and the [contrasting] empirically derived annealing temperature found to be optimal for each STR amplification."); Kimpton, p. 17, col. 3 ("Artifactual stutter bands caused by enzyme slippage during amplification were detected with a number of STR loci."). Thus, it is also evident from the failures of others that selection of successful loci combinations may require more than routine experimentation, *i.e.*, inventive skill. Fregeau, p. 104, col. 3 ("[o]ptimal conditions for the STR amplifications were empirically defined").

Therefore, because the references fail to teach or suggest all of the limitations of the claims, to provide a reasonable expectation of success when selecting STR loci capable of being co-amplified, co-amplifying sets of loci in a multiplex amplification reaction and evaluating the amplified alleles in the set to determine the alleles present at each of the loci in the set, and/or to provide a suggestion or motivation of how to combine their respective teachings to result in the claimed methods, Applicants submit that the Examiner has failed to establish a *prima facie* case that claims 21 and 24 are obvious in view of the cited references. In light of the arguments set forth above, including those provided by Ms. Sprecher in her declaration, Applicants respectfully request that the rejection of claims 21 and 24 under 35 U.S.C. § 103(a) in view of Caskey, GenBank, Fregeau, Kimpton and/or Urquhart be withdrawn.

Schumm, Fregeau, Kimpton and Urquhart

Claims 21 and 24 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Schumm et al. (U.S. Patent No. 5,783,406) ("Schumm"), in view of Fregeau, Kimpton and/or Urquhart. Schumm is characterized as teaching or suggesting all of the limitations of claims 21 and 24 except for the specifically claimed multiplex method for analyzing HUMTPOX, HUMCSF1PO and HUMVWFA31. The Examiner alleges, however, that it would have been *prima facie* obvious to modify the teachings of Schumm with the disclosures of Fregeau, Kimpton and/or Urquhart to obtain the claimed invention. The Examiner further alleges that "Schumm specifically provides the primer pairs for each of the STR loci" and the "ordinary artisan would have been motivated to expand the assay to the other loci taught by Schumm to enable further analysis and distinguishment of alleles." (Office Action, p. 17.)

For the reasons set forth above with respect to the rejection of claims over the combination Caskey, GenBank, Fregeau, Kimpton and Urquhart, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. Schumm does not cure the deficiencies of Fregeau, Kimpton and/or Urquhart in teaching or suggesting all of the limitations of the claims. Nowhere does Schumm teach or suggest any of the specifically claimed combinations of loci. Nor does Schumm provide any additional insight such that one having ordinary skill in the art would have a reasonable expectation of success of multiplexing the specifically claimed combinations of loci, particularly in light of all of the obstacles and problems known and discussed by those skilled in the art when selecting combinations of loci for multiplex analysis. Finally, Schumm does not provide a suggestion or motivation to combine its disclosure with those of Fregeau, Kimpton and/or Urquhart to result in the claimed methods. Nowhere do any of the cited references suggest or motivate one having ordinary skill in the art to combine their variously disclosed loci to result in the claimed methods.

Therefore, in light of the arguments set forth above, Applicants respectfully request that the rejection of claims 21 and 24 under 35 U.S.C. § 103(a) in view of Schumm, Fregeau, Kimpton and/or Urquhart be withdrawn.

Based on the foregoing, Applicants respectfully submit that claims 21 and 24 of the present application are in condition for allowance, and a favorable action thereon is respectfully requested. By responding to the rejections in this Office Action, Applicants do not concede that

any of the references cited herein are necessarily proper prior art under 35 U.S.C. §§ 102 and/or 103 and Applicants reserve the right to contest whether any of the cited references are indeed proper prior art should they decide to do so. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

Jill A. Fahrlander
Reg. No. 42,518

File No: 016026-9238-US02
Michael Best & Friedrich LLP
One South Pinckney Street
P. O. Box 1806
Madison, WI 53701-1806
608.257.3501